

*11
Core*

55. (Amended) A method of making a composition, the composition comprising at least one pellet comprising an inner core and a rate-controlling membrane, wherein the membrane determines the rate of drug release and means to prevent the release of the drug until the composition reaches the terminal ileum or a colon following oral administration of the composition, the method comprising:

- (a) providing a drug, wherein the drug has a free acid group, and a pKa in a range of 2.0 to 9.0;
- (b) making an alkali metal salt of the drug, wherein the salt of the drug has a higher solubility at pH 4.5 to 8.0 than a free acid form of the drug;
- (c) coating the salt onto the inner core; and
- (d) coating the rate-controlling membrane onto the salt,

wherein the composition prevents release of the drug until the composition reaches the terminal ileum or colon following oral administration of the composition.

REMARKS

Claims 29-57 are pending in this application. The Examiner has stated that claims 46 and 47 would be allowable, if rewritten in independent form to include the elements of the claims from which each depends.

Claims 54 and 55 have been amended to correct typographical errors, one of which was pointed out by the Examiner. No new matter is added by the amendments, as they are merely a correction of spelling. Marked up versions of the amended claims, showing the changes made is provided herewith pursuant to 37 C.F.R. § 1.121.

As a supplement to the arguments and reasoning set forth below, the applicant requests that the Examiner permit a telephonic interview between the Examiner and the applicant's representative to discuss the outstanding rejections to the claims and facilitate prosecution of this application. Therefore, it is requested that the Examiner contact the applicant to arrange for a suitable time for an interview prior to the issuance of any final rejection in this application.

Objection Under 35 U.S.C. § 132.

At page 2 of Paper No. 25, the Examiner has objected to the specification under 35 U.S.C. § 132, asserting that the Amendment filed May 13, 2002 introduced new matter into the disclosure. Specifically, the Examiner asserts that the new matter not supported by the original disclosure is: "poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.2", "poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.1", and "(poly ethyl acrylate, methyl methacrylate) 2:1." The Examiner states that he has considered the applicant's evidence but does not consider it relevant, as it is not dated prior to the filing date of the instant application.

As is stated in the prior response, the amendments made May 13, 2001 to which the Examiner refers are not new matter as a person of skill in the art would have been knowledgeable as to the generic compositions of each of the trademarked products at the time of filing. In support of this statement, the applicant supplies herewith a copy of a portion of the Handbook of Pharmaceutical Excipients, 2nd eds., Wade, et al., 1994. As can be seen, the 1994 publication date is prior to the effective filing date of this application in Great Britain (October 4, 1996), and thus is representative of the information with which a person of ordinary skill is charged. Specifically, this 1994 extract from the Handbook of Pharmaceutical Excipients shows that, like the reference provided in the prior response:

Eudragit™ RL 100 is poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride)1:2:0.2;

Eudragit™ RS 100/RS 30 D is poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.1; and

Eudragit™ NE 30 D is poly(ethyl acrylate, methyl methacrylate) 2:1.

Thus, the information inserted into the specification by the amendment of May 16, 2001 does not constitute new matter, as a person of skill at the time of filing of the application would have understood what generic composition was represented by use of the above-listed trademarks. Accordingly, it is requested that the Examiner reconsider and withdraw his objection on the basis that such subject matter was new matter under 35 U.S.C. § 132.

Correction of Typographical Error.

At page 3 of the Office Action, the Examiner has pointed out a spelling error in claim 55. Claim 55 has been amended to correct this spelling error. The applicant thanks the Examiner for his helpful comments.

Rejection Under 35 U.S.C. § 112, first paragraph – Enablement.

At pages 3-4, the Examiner has maintained his rejection of claims 29-45 and 48-57 under 35 U.S.C. § 112, first paragraph. In particular, as in the prior Office Action, the Examiner asserts that the specification does not enable a person skilled in the art to make and/or use the invention commensurate in scope of the claims. While it is unclear what aspect of the invention of the claims the Examiner considers to be non-enabled, it appears the Examiner is stating that the specification does not enable a rate controlling membrane, nor does it enable a means for preventing release of the drug until the composition reaches a terminal ileum or a colon following oral administration of the composition. Although the applicant's representative has previously confirmed with the Examiner by telephone that this is the basis of the Examiner's rejection, the applicant requests again that the Examiner confirm in writing in the next Office Action that these are the aspects of the claims which he considers non-enabling. Assuming the applicant has understood the Examiner correctly, the applicant traverses the rejection under 35 U.S.C. § 112.

It is well settled that, under U.S. patent law, a claimed invention is enabled by the specification if, based upon the disclosures of the specification and the knowledge of a person of skill in the art, such person would have been able to make and use the invention claimed. Because the applicant is entitled (and encouraged) to rely on the knowledge of a person of skill in the art when making his disclosure, a claim may be enabled even in cases where only a single specific embodiment is disclosed. M.P.E.P. 2164.01.

In the present situation, the recitations in the claims of (i) a rate controlling membrane, and (ii) a means for preventing release of the drug until the composition reaches a terminal ileum or a colon following oral administration of the composition are enabled, based upon the disclosures provided in the specification coupled with the knowledge of a person of skill in the art. First, as discussed previously, determination of which rate controlling

membrane(s) would be suitable for use in a specific embodiment of the claimed invention is well within the routine skill of a person of skill in the art. *See*, Declaration Under 37 C.F.R. § 1.132 of Peter James Watts at ¶ 5, (hereinafter "Dec."), provided with the prior response. Such rate controlling membranes are disclosed in the literature, which is known to the person of skill in the art, such as, for example, Hogan J., "Film Coatings for Controlled Release Multiparticulate Dosage Forms," Multiparticulate Controlled Release Oral Dosage Forms: Technology and Biopharmaceutics, eds. Melia et al., Scottish Academic Press, Edinburgh, pages 36-49 (1994), and Bauer, et al., Coated Pharmaceutical Dosage Forms, CRC Press, Boca Raton, at least at pages 69-70 (1998), copies of which were provided to the Examiner.

In addition, rate controlling membranes are disclosed in the specification at pages 7 and 8. Based upon what is known in the prior art and the disclosures of the instant application, a person of skill would recognize that the thickness, pH, permeability, and degradability of the rate controlling membrane for use in the invention would necessarily vary, depending on the polymer used in the membrane, the solubility of the drug in question, and the duration of the release desired in the coated formulation, and could easily have made such determinations without undue experimentation based upon the instruction provided in the art and/or the specification. Thus, those portions of the claims reciting rate controlling membrane(s) are fully enabled by the specification.

Similarly, with respect to the recited claim element "means to prevent release of a drug," such claim elements are fully enabled by the specification, for example, at pages 8-11. Additionally, such means are disclosed and discussed in the art, and accordingly, well known to the person of skill in the art. *See, e.g.*, Hardy, J.G., et al., eds., Drug Delivery to the Gastrointestinal Tract, Halsted Press, New York, page 92 (1989), a copy of which was provided to the Examiner.

The Examiner argues that, with respect to each of these elements, the applicant's arguments are unpersuasive because, as is shown in the prior art, similar means, membranes and/or coating compositions give different rates of release, and because of such differences, the level of experimentation is undue. To the contrary, that a person of skill may need to engage in some level of experimentation to practice the invention does not render the claims

per se non-enabled, as long as the experimentation is not excessive. In the case of the instant claims, as the specification provides guidance as to some suitable membranes and discusses the desired properties of the invention, a person of skill charged with the information known at the time of filing of the application, as, for example, demonstrated by the art references discussed above, would have been able to make and use the invention.

In view of the foregoing, it is respectfully requested that the Examiner withdraw the § 112, first paragraph, rejections and not apply them to the new claims.

Rejection Under 35 U.S.C. § 112, first paragraph – Written Description.

At page 4 of the Office Action, the Examiner has rejected claim 34 under 35 U.S.C. § 112, first paragraph, asserting that the specification does not provide written description support of claim 34. The applicant respectfully traverses this rejection.

As discussed in the prior response, the composition originally recited on claim 34 in claim 34 was referred to by trademark. A person of skill in the art at the time the application was filed, would have known what the generic chemistry of the composition represented by the trademark was. In support of this argument, the applicant has provided the excerpt from the Handbook of Pharmaceutical Excipients, as discussed above in relation to the objection to the specification. Accordingly, in view of this submission, it is respectfully requested that the Examiner reconsider and withdraw the rejection with respect to claim 34.

Rejection Under 35 U.S.C. § 112, second paragraph.

At pages 3-4, the Examiner has maintained the rejection of claims 29-45 and 48-57 under 35 U.S.C. § 112, second paragraph, asserting that such claims are “incomplete for omitting essential elements and steps.” In particular, the Examiner has articulated that such allegedly essential elements and steps include the thickness of the membrane and the pH solubility of the membrane. Additionally, the Examiner has rejected claim 19 asserting that it omits the recitation of an effective amount of a drug.

As a threshold matter, the applicant notes that claim 19 has been cancelled in the prior response. As discussed in that prior response, the corresponding new claim, claim 57, includes a recitation that the “composition contain[s] an effective amount of a drug.” Thus, the

Examiner's rejection is no longer applicable and it is respectfully requested that the Examiner reconsider and withdraw it.

With regard to the § 112 rejection of the remaining claims on the ground that the claims must necessarily include the pH solubility and thicknesses of the membrane, the applicant respectfully traverses the rejection. A person of skill in the art at the time the application was filed would have recognized that the pH solubility and the thickness of the membrane would necessarily vary, depending on the polymer used in the membrane, the solubility of the drug in question, and the duration of release desired in the coated formulation. That such elements may be varied depending on numerous variables is part of the invention, and because such variations are well within the purview of a person of skill in the art, it is not necessary that the specific pH solubility and/or thicknesses be recited in the claims.

Omission of the membrane pH solubility and thicknesses does not render the claim indefinite, the Examiner's imposition of such requirement is an attempt to impermissibly and unnecessarily require the applicant to restrict the claims to a subject matter lesser in scope than that to which he is entitled. Accordingly, it is requested that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 112, second paragraph.

CONCLUSION

In view of the foregoing, reconsideration and allowance of claims 29-45 and 48-57 at the earliest opportunity is earnestly solicited. As a supplement to the information presented above, it is requested that the Examiner contact the undersigned to arrange for an appropriate time for further discussion.

Respectfully submitted,

PETER JAMES WATTS

18 November 2002

(Date)

By:



KRISTYNE A. BULLOCK

Registration No. 42,371

AKIN, GUMP, STRAUSS, HAUER & FELD, L.L.P.

One Commerce Square

2005 Market Street - Suite 2200

Philadelphia, PA 19103-7086

Telephone: (215) 965-1200

Direct Dial: (215) 965-1348

Facsimile: (215) 965-1210

E-Mail: kbullock@akingump.com

Attorney for Applicant

KAB/vj
Enclosures

Petition for Extension of Time (one month)

Marked Up Version of Claims 54 and 55

Handbook of Pharmaceutical Excipients, 2nd eds., Wade, et al., 1994 at 363.

Marked Up Version of Claim 54 and 55
After Amendment Filed November 18, 2002

54. (Amended) The method of claim 50, wherein the composition is coated with an enteric layer that dissolves within the small intestine to allow exposure of the membrane to a liquid of the terminal [illum] ileum or colon.

55. (Amended) A method of making a composition, the composition comprising at least one pellet comprising an inner core and a rate-controlling membrane, wherein the membrane determines the rate of drug release and means to prevent the release of the drug until the composition reaches the terminal ileum or a colon following oral administration of the composition, the method comprising:

- (a) providing a drug, wherein the drug has a free acid group, and a pKa in a range of 2.0 to 9.0;
- (b) making an alkali metal salt of the drug, wherein the salt of the drug has a higher solubility at pH 4.5 to 8.0 [that] than a free acid form of the drug;
- (c) coating the salt onto the inner core; and
- (d) coating the rate-controlling membrane onto the salt,

wherein the composition prevents release of the drug until the composition reaches the terminal ileum or colon following oral administration of the composition.

Handbook of PHARMACEUTICAL EXCIPIENTS

Second Edition

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Ainley Wade and Paul J Weller

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etic, and food products.

Table I: Chemical name and CAS registry number of polymethacrylates.

Chemical name	Trade name	CAS number
Poly(butyl methacrylate, (2-dimethyl aminoethyl) methacrylate, methyl methacrylate) 1:2:1	<i>Eudragit E 100</i> <i>Eudragit E 12.5</i> <i>Eudragit NE 30 D</i> (formerly <i>Eudragit 30 D</i>)	[24938-16-7] [9010-88-2]
Poly(ethyl acrylate, methyl methacrylate) 2:1	<i>Eudragit L 100</i> <i>Eudragit L 12.5</i> <i>Eudragit L 12.5 P</i> <i>Eudragit L 30 D-55</i> <i>Eudragit L 100-55</i>	[25806-15-1] [25212-88-8]
Poly(methacrylic acid, methyl methacrylate) 1:1	<i>Eudragit S 100</i> <i>Eudragit S 12.5</i> <i>Eudragit S 12.5 P</i> <i>Eudragit RL 100</i> <i>Eudragit RL PO</i>	[25086-15-1] [33434-24-1]
Poly(methacrylic acid, ethyl acrylate) 1:1	<i>Eudragit RL 30 D</i> <i>Eudragit RL 12.5</i> <i>Eudragit RS 100</i> <i>Eudragit RS PO</i>	[33434-24-1]
Poly(methacrylic acid, methyl methacrylate) 1:2	<i>Eudragit RS 30 D</i> <i>Eudragit RS 12.5</i>	
Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.2		
Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.1		

Eudragit S-100 are white free flowing powders with at least 95% of dry polymers.

Eudragit RL and *Eudragit RS*, also referred to as ammonio-methacrylate copolymers in the USPNF monograph, are copolymers synthesized from acrylic acid and methacrylic acid esters with *Eudragit RL* (type A) having 10% of functional quaternary ammonium groups and *Eudragit RS* (type B) having 5% of functional quaternary ammonium groups. The ammonium groups are present as salts and give rise to pH-independent permeability of the polymers. Both polymers are water-insoluble, and films prepared from *Eudragit RL* are freely permeable to water, whereas, films prepared from *Eudragit RS* are only slightly permeable to water. They are available as 12.5% ready-to-use solutions in propan-2-ol/acetone (60:40). Solutions are colorless or slightly yellow in color, and may be clear or slightly turbid; they have an odor characteristic of the solvents. Solvent-free granules (*Eudragit RL 100* and *Eudragit RS 100*) contain $\geq 97\%$ of the dried weight content of the polymer.

Eudragit RL PO and *Eudragit RS PO* are fine, white powders with a slight amine-like odor. They are characteristically the same polymers as *Eudragit RL* and *RS*. They contain $\geq 97\%$ of dry polymer.

Eudragit RL 30 D and *Eudragit RS 30 D* are aqueous dispersions of copolymers of acrylic acid and methacrylic acid esters with a low content of quaternary ammonium groups. The dispersions contain 30% polymer. The quaternary groups occur as salts and are responsible for the permeability of films made from these polymers. Films prepared from *Eudragit RL 30 D* are readily permeable to water and to dissolved active substances, whereas films prepared from *Eudragit RS 30 D* are less permeable to water. Film coatings prepared from both polymers give pH-independent release of active substance. Plasticizers are usually added to improve film properties.

Eudragit NE 30 D is an aqueous dispersion of a neutral copolymer consisting of polymethacrylic acid esters. The dispersions are milky-white liquids of low viscosity and have a weak aromatic odor. Films prepared from the lacquer swell in water, to which they become permeable. Thus, films produced are insoluble in water, but give pH-independent drug release.

Eudragit L 30 D-55 is an aqueous dispersion of an anionic copolymer based on methacrylic acid and acrylic acid ethyl ester. The polymer corresponds to USPNF methacrylic acid copolymer, type C. The ratio of free carboxyl groups to ester groups is 1:1. Films dissolve above pH 5.5 forming salts with alkalis, thus affording coatings which are insoluble in gastric media, but soluble in the small intestine.

Eudragit L 100-55 (prepared by spray-drying *Eudragit L 30 D-55*) is a white, free-flowing powder which is redispersible in water to form a latex which has properties similar to *Eudragit L 30 D-55*.

9. Pharmacopeial Specifications

Specifications for methacrylic acid copolymers (*Eudragit L*, *S* and *L 30 D-55*).

Test	USPNF XVII (Suppl 6)
Identification	+
Viscosity	
Type A	50-200 mPa s
Type B	50-200 mPa s
Type C	100-200 mPa s
Loss on drying	
Type A	$\leq 5.0\%$
Type B	$\leq 5.0\%$
Type C	$\leq 3.0\%$
Residue on ignition	
Type A	$\leq 0.1\%$
Type B	$\leq 0.1\%$
Type C	$\leq 0.4\%$
Arsenic	$\leq 2 \text{ ppm}$
Heavy metals	$\leq 0.002\%$
Monomers	$\leq 0.3\%$
Assay of methacrylic acid units (dried basis)	
Type A	46.0-50.6%
Type B	27.6-30.7%
Type C	46.0-50.6%